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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS:	Lorraine E. Pena, *et al.*	)	DOCKET NO.:	6193/1
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SERIAL NO.:	10/072,492	)	GROUP ART UNIT	Unknown
		)		
FILED:	February 5, 2002	)	EXAMINER	Unknown

TITLE: COMPOSITION AND METHOD FOR RECTAL DELIVERY OF A LINCOSAMIDE ANTIBACTERIAL DRUG

CERTIFICATE OF MAILING

I hereby certify that this communication and recited enclosures are being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Box Missing Parts, Washington, DC 20231 on: June 27, 2002.

Signed: Bernadette J. Harper

Assistant Commissioner for Patents
Box Missing Parts
Washington, DC 20231

COPY OF PAPERS ORIGINALLY FILED

Sir:

PRELIMINARY AMENDMENT AND RESPONSE TO NOTICE TO FILE MISSING PARTS

In response to a Notice to File Missing Parts of Nonprovisional Application, mailed February 28, 2002, Applicants hereby petition, under 37 CFR §1.136(a) for a two month extension of time to respond to the Notice, and ask that the $130.00 fee set forth for the extension under 37 CFR §1.16(l) be charged to Deposit Account No. 21-0718. Please charge any additional fees or credit any amounts associated with this response to that same Deposit Account. Enclosed herewith, please find an executed Oath or Declaration, cited as missing in the Notice. Enclosed also, please find substitute drawings, amended as described in the Preliminary Amendment, below, with the descriptive legends removed or reduced to contain as few words as possible, in accordance with 37 CFR §1.84(o). Applicants respectfully submit that, with the submission of the enclosed Oath or Declaration and replacement Drawings, all the requirements set forth in the Notice to file Missing Parts have been met.

The Oath or Declaration incorporated the following Preliminary Amendment, by reference:

I. IN THE SPECIFICATION

Please amend the specification as shown in the following replacement paragraphs, in accordance with 37 CFR §1.121(b)(ii). Marked up versions of each of the replacement paragraphs are attached to this response, beginning on a separate sheet.

Please replace the paragraph beginning on page 1, line 23 with the following:

Clindamycin has long been recognized as being particularly effective in the treatment of staphylococcal infections. Several commercial formulations of clindamycin designed for oral administration can be found on the market, including CLEOCIN® HCL (Pharmacia Corporation, NJ, USA), an oral formulation of clindamycin hydrochloride designed for adults, and CLEOCIN® PEDIATRIC (Pharmacia Corp.), an oral formulation of clindamycin palmitate hydrochloride designed for children. In such formulations clindamycin hydrochloride and clindamycin palmitate hydrochloride are hydrolyzed to clindamycin free base in the gastrointestinal tract of a subject, prior to being absorbed into the bloodstream.

Please replace the paragraph beginning on page 2, line 19 with the following:

Formulations, such as vaginal suppositories or topical creams, that permit one to administer a drug to a subject through the vagina offers several advantages over oral and parenteral means, described above. See, for example, vaginal suppositories of clindamycin disclosed in International Application No. PCT/US00/19533, published as WO 01/10407, incorporated by reference herein. The present application claims priority to the same U.S. provisional application cited therein, through a U.S. counterpart of the International Application, U.S. Patent Application No. 09/619,930. WO 01/10407 does not disclose the administration of any lincosamides other than clindamycin, nor does it suggest that any such composition be rectally administered. Depending upon the composition of the formulation, such formulations enable one to treat bacterial infections in the vagina of a subject alone, and/or to introduce the active agent into the blood stream and into various other parts and systems of the subject. Naturally, vaginal administration is only available to a certain portion of the population of any given subject species.

Please replace the paragraph beginning on page 3, line 1 with the following:

The rectal route of administration offers several advantages over other means of administration, including the availability of the means of delivery to all members of a species, regardless of gender, throat size, or aversion to needles. Various types of suppositories have been described as being useful for rectal delivery of any one of a number of different active

agents into a subject, including lincosamides, such as clindamycin or lincomycin. See, for example, U.S. Patent No. 4,289,757 by E. Myles Glen; EP 0 206 947 by Jose Alexander; WO 99/29299 by Rudolf Linder; and U.S. Patent No. 4,464,466 by Alexander Argoudelis.

Please replace the paragraph beginning on page 3, line 29 with the following:

In one embodiment, the present invention is a suppository composition for rectal administration of a lincosamide antibacterial drug, the composition comprising an antimicrobially effective amount of the lincosamide dispersed in a Hard Fat suppository base, wherein the lincosamide is in the form of solid particles. Suppositories of the present invention can be used to effect systemic delivery of a lincosamide to a subject, by rectal administration.

Please replace the paragraph beginning on page 5, line 9 with the following:

Figure 1 shows an x-ray diffraction pattern of the different polymorphic transitions that a Hard Fat NF suppository base containing clindamycin will go through over time. The peaks at 15-25° 2θ represent the peaks associated with the polymorphic transition of the base, wherein A = α, B = α', and C= β.

Please replace the paragraph beginning on page 5, line 12 with the following:

Figure 2 is a flow chart illustrating a method of manufacturing lincosamide rectal suppositories of the present invention.

Please replace the paragraph beginning on page 5, line 24 with the following:

In one embodiment, the composition comprises an antimicrobially effective amount of a lincosamide or a pharmaceutically acceptable salt or ester thereof dispersed in a Hard Fat base. The Hard Fat suppository base used in the compositions of the present invention is preferably a Hard Fat NF grade suppository base. Hard Fat bases, particularly, Hard Fat NF suppository bases, provide an active agent having high stability and efficacy in treating disorders caused by bacteria.

Please replace the paragraph beginning on page 6, line 1 with the following:

As used herein, the term "Hard Fat base" refers to a mixture of glyceride esters of higher saturated fatty acids. The mixture of triglycerides, diglycerides and monoglycerides making up a Hard Fat may be obtained either by esterification of fatty acids of natural origin

with glycerol or by transesterification of natural fats. Each type of Hard Fat is characterised by its melting point, its hydroxyl value and its saponification value.

Please replace the paragraph beginning on page 7, line 25 with the following:

The uses, properties and methods of synthesis of clindamycin are set forth in U.S. Patent 3,969,516, Stoughton, issued July 13, 1976; U.S. Patent 3,475,407, Bierkenmeyer, issued in 1969; U.S. Patent 3,487,068, issued in 1969; U.S. Patent 3,509,127 and 3,544,551, Kagan and Magerlein, issued in 1970; U.S. Patent 3,513,155, Bierkenmeyer and Kagan, issued in 1970; Morozowich and Sinkula, U.S. Patent 3,580,904 issued in 1971 and 3,655,885 issued in 1972; U.S. Patent 3,714,141, issued in 1973; U.S. Patent 4,568,741 issued in 1986; U.S. Patent 4,710,565, issued in 1984; (all of the foregoing patents being incorporated herein by reference).

Please replace the paragraph beginning on page 8, line 22 with the following:

Lincomycin, its characteristics, and methods of synthesis thereof are set forth in many references, including but not limited to, U.S. Patent No. 3,086,912, in U.S. Patent No. 3,676,302 by Jeronimo Visser, incorporated herein by reference. Methods of synthesis of and descriptions of lincomycin derivative antibiotics suitable for use in the compositions of the present invention are set forth in many references, including, but not limited to, U.S. Patent No. 3,329,568 by Alexander Argoudelis, in U.S. Patent No. 3,359,164 by Alexander Argoudelis, in U.S. Patent No. 3,361,739 by Alexander Argoudelis, in U.S. Patent No. 3,395,139 by Donald Mason.

Please replace the paragraph beginning on page 9, line 8 with the following:

All three preferred types of lincosamides described above, i.e. clindamycin, lincomycin, and pirlimycin, have been administered to various types of animals, as antibiotics. All three have also been used as growth enhancers for meat producing animals. See, for example studies discussed in WO 88/09130.

Please replace the paragraph beginning on page 9, line 12 with the following:

The lincosamide is preferably present as a solid, in particulate form. The size of the particles depends upon the solubility of the particular lincosamide used, with smaller particles needed for less soluble forms of lincosamides. The volume mean diameter of the solid particles of lincosamides are preferably at least about 0.5 μm to about 500 μm, more

preferably 0.5 μm to about 300 μm, even more preferably 0.5 μm to about 150 μm, even more preferably about 0.5 μm to about 10 μm. The particles of the lincosamide are preferably dispersed in a pharmaceutically acceptable carrier, in which the lincosamide is poorly soluble, wherein the composition is adapted for rectal administration. The pharmaceutically acceptable carrier preferably comprises a Hard Fat.

Please replace the paragraph beginning on page 11, line 1 with the following:

The total weight of typical rectal suppositories for human subjects preferably range in size from about 0.5 g to about 10 g, preferably from about 1 g to about 5 g, and most preferably from about 2 g to about 3 g. Human rectal clindamycin suppository compositions would generally be in the range of 0.1% to 60% by weight of clindamycin, preferably 0.5% to 30%, more preferably 1.5% to 10%, and most preferably 1.5% to 7.5% of clindamycin. The percent by weight of lincosamide in the most preferred suppositories of the present invention depends upon the total weight of the suppository and the dose required for systemic treatment of an infection of harmful gram-positive bacteria in subject(s) to be treated therewith.

Please replace the paragraph beginning on page 13, line 27 with the following:

If the particle size of a bulk sample of a lincosamide is greater than 10 μm, it may be reduced in particle size by any conventional means. However, it is preferably milled using a pulverizing rotary mill or air jet micronizer. With the exception of particle size, the physical and chemical characteristics of the milled drug are preferably the same as the unmilled drug.

Please replace the paragraph beginning on page 14, line 1 with the following:

A particularly preferred embodiment of the invention is a suppository comprising a lincosamide having a particle size of 10 μm or less dispersed in a Hard Fat NF suppository base. The suppository is solid at room temperature, and has a flow point of 37 °C or less after reaching the ß polymorphic form. In the more preferred embodiment, the Hard Fat NF is a mixture of glyceride esters of vegetable C_{12}-C_{18} saturated fatty acids, the majority of which are triglycerides. In the most preferred embodiment, the Hard Fat NF meets the specifications described previously above.

Please replace the paragraph beginning on page 17, line 21 with the following:

A batch of 120 clindamycin suppositories, each of which was configured to deliver a single dose of clindamycin for treatment of an adult human, was produced using the following procedure:

1. 264.00 g of WITEPSOL H-32 Hard Fat NF base was melted in a manufacturing kettle by heating to 40+2°C. The temperature of the molten suppository base was maintained at 40+2°C throughout the manufacturing procedure.

2. 36.0 g of clindamycin was added to the kettle and mixed and homogenized to obtain a uniform dispersion.

3. Each cavity of the suppository mold was filled with 2.5 g of the drug dispersion.

4. The suppository base was cooled over night at room temperature. The next morning the hardened suppositories were removed from the mold.

II. IN THE CLAIMS

Please amend claim 7 to read as follows:

7. (Amended) The composition of claim 6 wherein the clindamycin is present in said composition in an amount from about 1.5 % by weight of the entire composition to about 7.5% by weight of the entire composition.

III. IN THE DRAWINGS

Please replace the drawing sheets for Figures 1 and 2 with the enclosed drawing sheets.

IV. REMARKS

Applicants respectfully submit that none of the amendments introduced herein introduces new matter into the above-cited application, as filed. Most of the amendments are either introduced in order to correct typographic errors (e.g., correcting the spellings of certain words, correcting typographic errors in citations to certain patents and published applications, and changing μM to μm when used to refer to particle size), to correct obvious substitutions of one word for another (e.g., when one lincosamide was substituted for another or for "lincosamide" in the specification or in the upper right hand box of Figure 2), and to correct the wording of claim 7 to remove a phrase that made its meaning otherwise unclear. Specifically, claim 7 was amended to remove a phrase describing the amount of clindamycin present in that particular embodiment of the composition in terms of a weight range, when the

amount of clindamycin was already described in the same claim in terms of percent by weight of the composition.

In addition to the changes described above, the legends of Figures 1 and 2 were also amended to remove descriptions therefrom, in response to the Notice to File Missing Parts. Details about the figures removed from the legends of Figures 1 and 2 were added to the descriptions of each figure in the Brief Description of the Drawings section of the application, on page 5 of the specification.

V. SUMMARY

Applicants respectfully submit that none of the amendments to the specification, drawings, or claims introduced herein introduce any new matter into the application as filed, for reasons given above. All of the amendments introduced herein merely clarify the language of the application and bring the drawings into compliance with formal requirements set forth in the Notice to File Missing Parts. This Preliminary Amendment is incorporated by reference into the Oath and Declaration filed herewith.

Applicants submit that the present response and enclosed documents are completely responsive to the Notice to File Missing Parts. Therefore, Applicants respectfully request that the above-identified patent application be forwarded to the Examining Division.

Respectfully submitted,

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Tel. (847) 581-6996

Address correspondence to:
Pharmacia Corporation
Patent Department
800 N Lindbergh Boulevard – O4E
St Louis, MO 63167

Enclosures
Copy of Notice of Missing Parts
Oath or Declaration
Replacement Figures 1 and 2

MARKED-UP VERSIONS OF AMENDMENTS

I. IN THE SPECIFICATION

Paragraphs amended as described in replacement paragraphs, above, are shown below in marked-up format, in accordance with 37 CFR §1.121(b)(iii), with underlining used to show insertions and with square brackets ("[]") used to indicate deletions.

The paragraph beginning on page 1, line 23 has been amended as follows:

Clindamycin has long been recognized as being particularly effective in the treatment of staphylococcal infections. Several commercial formulations of clindamycin designed for oral administration can be found on the market, including CLEOCIN® HCL (Pharmacia Corporation, NJ, USA), an oral formulation[s] of clindamycin hydrochloride designed for adults, and CLEOCIN® PEDIATRIC (Pharmacia Corp.), an oral formulation of clindamycin palmitate hydrochloride designed for children. In such formulations clindamycin hydrochloride and clindamycin palmitate hydrochloride are hydrolyzed to clindamycin free base in the gastrointestinal tract of a subject, prior to being absorbed into the bloodstream.

The paragraph beginning on page 2, line 19 has been amended as follows:

Formulations, such as vaginal suppositories or topical creams, that permit one to administer a drug to a subject through the vagina offers several advantages over oral and parenteral means, described above. See, for example, vaginal suppositories of clindamycin disclosed in International Application No. PCT/US00/19533, published as WO 01/10407, incorporated by reference herein. The present application claims priority to the same U.S. provisional application cited therein, through a U.S. counterpart of the International Application, U.S. Patent Application No. 09/619,930. WO 01/10407 does not disclose the administration of any lincosamides other than clindamycin, nor does it suggest that any such composition be rectally administered. Depending upon the composition of the formulation, such formulations enable one to treat bacterial infections in the vagina of a subject alone, and/or to introduce the active agent into the blood stream and into various other parts and systems of the subject. Naturally, vaginal administration is only available to a certain portion of the population of any given subject species.

The paragraph beginning on page 3, line 1 has been amended as follows:

The rectal route of administration offers several advantages over other means of

administration, including the availability of the means of delivery to all members of a species, regardless of gender, throat size, or aversion to needles. Various types of suppositories have been described as being useful for rectal delivery of any one of a number of different active agents into a subject, including lincosamides, such as clindamycin or lincomycin. See, for example, U.S. Patent No. 4,289,757 by E. Myles Glen; E[O]P 0 206 947 by Jose Alexander; WO 99/29299 by Rudolf Linder; and U.S. Patent No. 4,464,466 by Alexander Argoudelis.

The paragraph beginning on page 3, line 29 has been amended as follows:

In one embodiment, the present invention is a suppository composition for rectal administration of a lincosamide antibacterial drug, the composition comprising an anti[b]microbially effective amount of the lincosamide dispersed in a Hard Fat suppository base, wherein the lincosamide is in the form of solid particles. Suppositories of the present invention can be used to effect systemic delivery of a linco[mycin]samide to a subject, by rectal administration.

The paragraph beginning on page 5, line 9 has been amended as follows:

Figure 1 shows an x-ray diffraction pattern of the different polymorphic transitions that a Hard Fat NF suppository base containing clindamycin will go through over time. The peaks at 15-25° 2θ represent the peaks associated with the polymorphic transition of the base, wherein A = α, B = α', and C= β.

The paragraph beginning on page 5, line 12 has been amended to read as follows:

Figure 2 is a flow chart illustrating a method of manufacturing lincosamide rectal [schematic of a system for preparing] suppositories of the present invention.

The paragraph beginning on page 5, line 24 has been amended as follows:

In one embodiment, the composition comprises an antimicrobially effective amount of a lincosamide or a pharmaceutically acceptable salt or ester thereof dispersed in a Hard Fat base. The Hard Fat suppository base used in the compositions of the present invention is preferably a Hard [H]Fat NF grade suppository base. Hard Fat bases, particularly, Hard Fat NF suppository bases, provide an active agent having high stability and efficacy in treating disorders caused by bacteria.

The paragraph beginning on page 6, line 1 has been amended as follows:

As used herein, the term "Hard Fat base" refers to a mixture of glyceride esters of higher saturated fatty acids. The mixture of triglycerides, diglycerides and monoglycerides

making up a Hard Fat may be obtained either by esterification of fatty acids of natural origin with glycerol or by transesterification of natural fats. Each type of Hard Fat is characterised by its melting point, its hydroxyl value and its saponification value.

The paragraph beginning on page 7, line 25 has been amended as follows:

The uses, properties and methods of synthesis of clindamycin are set forth in U.S. Patent 3,969,516, Stoughton, issued July 13, 1976; U.S. Patent 3,475,407, Bierkenmeyer, issued in 1969; U.S. Patent 3,487,068, issued in 1969; U.S. Patent 3,509,127 and 3,544,551, Kagan and Magerlein, issued in 1970; U.S. Patent 3,513,155, Bierkenmeyer and Kagan, issued in 1970; Morozowich and Sinkula, U.S. Patent 3,5[0]80,904 issued in 1971 and 3,655,885 issued in 1972; U.S. Patent 3,714,141, issued in 1973; U.S. Patent 4,568,741 issued in 1986; U.S. Patent 4,710,565, issued in 1984; (all of the foregoing patents being incorporated herein by reference).

The paragraph beginning on page 8, line 22 has been amended as follows:

Lincomycin, its characteristics, and methods of synthesis thereof are set forth in many references, including but not limited to, U.S. Patent No. 3,086,912, in U.S. Patent No. 3,676,302 by Jeronimo Visser, incorporated herein by reference. Methods of synthesis of and descriptions of lincomycin derivative antibiotics suitable for use in the compositions of the present invention are set forth in many references, including, but not limited to, U.S. Patent No. 3,329,568 by Alexander Argoudelis, in U.S. Patent No. 3,359,164 by Alexander Argoudelis, in U.S. Patent No. 3,361,73[8]9 by Alexander Argoudelis, in U.S. Patent No. 3,395,139 by Donald Mason.

The paragraph beginning on page 9, line 8 has been amended as follows:

All three preferred types of lincosamides described above, i.e. clin[c]damycin, lincomycin, and pirlimycin, have been administered to various types of animals, as antibiotics. All three have also been used as growth enhancers for meat producing animals. See, for example studies discussed in WO 88/09130.

The paragraph beginning on page 9, line 12 has been amended as follows:

The lincosamide is preferably present as a solid, in particulate form. The size of the particles depends upon the solubility of the particular lincosamide used, with smaller particles needed for less soluble forms of lincosamides. The volume mean diameter of the solid

particles of lincosamides are preferably at least about 0.5 μm to about 500 μm, more preferably 0.5 μm to about 300 μm, even more preferably 0.5 μm to about 150 μm, even more preferably about 0.5 μm to about 10 μm. The particles of the lincosamide are preferably dispersed in a pharmaceutically acceptable carrier, in which the lincosamide is poorly soluble, wherein the composition is adapted for rectal administration. The pharmaceutically acceptable carrier preferably comprises a Hard Fat.

The paragraph beginning on page 11, line 1 has been amended as follows:

The total weight of typical rectal suppositories for human subjects preferably range in size from about 0.5 g to about 10 g, preferably from about 1 g to about 5 g, and most preferably from about 2 g to about 3 g. Human rectal clindamycin suppository compositions would generally be in the range of 0.1% to 60% by weight of clindamycin, preferably 0.5% to 30%, more preferably 1.5% to 10%, and most preferably 1.5% to 7.5% of clindamycin. The percent by weight of lincosamide in the most preferred suppositories of the present invention depends upon the total weight of the suppository and the dose required for systemic treatment of an infection of [a] harmful gram-positive bacteria in subject(s) to be treated therewith.

The paragraph beginning on page 13, line 27 has been amended as follows:

If the particle size of a bulk sample of a lincosamide is greater than 10 μ[M]m, it may be reduced in particle size by any conventional means. However, it is preferably milled using a pulverizing rotary mill or air jet micronizer. With the exception of particle size, the physical and chemical characteristics of the milled drug are preferably the same as the unmilled drug.

The paragraph beginning on page 14, line 1 has been amended as follows:

A particularly preferred embodiment of the invention is a suppository comprising a lincosamide having a particle size of 10 μ[M]m or less dispersed in a Hard Fat NF suppository base. The suppository is solid at room temperature, and has a flow point of 37 °C or less after reaching the ß polymorphic form. In the more preferred embodiment, the Hard Fat NF is a mixture of glyceride esters of vegetable C_{12}-C_{18} saturated fatty acids, the majority of which are triglycerides. In the most preferred embodiment, the Hard Fat NF meets the specifications described previously above.

The paragraph beginning on page 17, line 21 (Example 6) has been amended as follows:

A batch of 120 clindamycin suppositories, each of which was configured to deliver a single dose of [lincomycin]clindamycin for treatment of an adult human, was produced using the following procedure:

1. 264.00 g of WITEPSOL H-32 Hard Fat NF base was melted in a manufacturing kettle by heating to 40+2°C. The temperature of the molten suppository base was maintained at 40+2°C throughout the manufacturing procedure.

2. 36.0 g of clindamycin was added to the kettle and mixed and homogenized to obtain a uniform dispersion.

3. Each cavity of the suppository mold was filled with 2.5 g of the drug dispersion.

4. The suppository base was cooled over night at room temperature. The next morning the hardened suppositories were removed from the mold.

II. IN THE CLAIMS

Claim 7 has been amended as follows:

7. (Amended) The composition of claim 6 wherein [said composition contains 50 to 150 mg of] the clindamycin is present in said composition in an amount from about 1.5 % by weight of the entire composition to about 7.5% by weight of the entire composition.